OFFICE OF NAVAL RESEARCH

CONTRACT N00014-88-C-0118
CONTRACT N00014-94-C-0149

TECHNICAL REPORT 95-02

AUTOLOGOUS ERYTHROCYTE INFUSION MAY NOT ATTENUATE THE DECREMENT IN VO2MAX AT HIGH ALTITUDE

BY

A.J. YOUNG, M.N. SAWKA, S.R. MUZA, R. BOUSHEL, T. LYONS, P.B. ROCK, B.J. FREUND, R. WATERS, A. CYMERMAN, K.B. PANDOLF, AND C.R. VALERI

NAVAL BLOOD RESEARCH LABORATORY
BOSTON UNIVERSITY SCHOOL OF MEDICINE
615 ALBANY STREET
BOSTON, MA 02118

10 JANUARY 1995

AUTOLOGOUS ERYTHROCYTE INFUSION MAY NOT ATTENUATE THE DECREMENT IN VO_{2MAX} AT HIGH ALTITUDE

Andrew J. Young, Michael N. Sawka, Stephen R. Muza, Robert Boushel, Timothy Lyons, Paul B. Rock, Beau J. Freund, Ray Waters, Allen Cymerman, Kent B. Pandolf and C. Robert Valeri

US Army Research Institute of Environmental Medicine, Natick, MA 01760-5007; and Naval Blood Research Laboratory, Boston University Medical Center, Boston, MA 02118

Running Head: Blood Doping at High Altitude

Address for Correspondence:

Andrew J. Young, Ph.D.
Thermal Physiology and Medicine Division
USARIEM
Natick, MA 01760-5007
Telephone: 508-651-5141
Fax: 508-651-5298

ABSTRACT

This study investigated whether autologous erythrocyte infusion would ameliorate the decrement in maximal oxygen uptake (VO_2MAX) experienced by lowlanders when they ascend to high altitude. Sixteen men's VO_2MAX was measured (treadmill running) at sea level (SL), and on the first (HA1) and ninth (HA9) day of high altitude (4300 m) residence. After VO_2MAX was measured at SL, subjects were divided into two matched groups (N = 8). Twenty-four hrs before ascent to high altitude, the experimental group (ER) received a 700 ml infusion of autologous erythrocytes and saline (42% hematocrit), while the control group (CON) received only saline. The VO_2MAX ($\bar{X}\pm sd$) of ER (54 $\pm$ 3 $ml \cdot kg^{-1} \cdot min^{-1}$) and CON (52 $\pm$ 4 $ml \cdot kg^{-1} \cdot min^{-1}$) did not differ at SL before infusion. The decrement in VO_2MAX on HA1 was not different for ER (25 $\pm$ 3%) and CON (28 $\pm$ 5%), despite higher ($P < 0.01$) arterial hematocrit (HCT), hemoglobin concentration (Hb) and arterial oxygen content (C_aO_2) in ER. By HA9, there were no longer any differences in HCT, Hb, or C_aO_2 between groups. No change in VO_2MAX occurred between HA1 and HA9 for either ER or CON. Thus, despite increasing arterial oxygen carrying capacity, autologous erythrocyte infusion did not ameliorate the decrement in Vo_2max at 4300 m altitude.

KEY WORDS: blood doping, exercise, hypoxia, oxygen transport

INTRODUCTION

Barometric pressure decreases with increasing altitude, and partial pressure of oxygen in the atmosphere declines in parallel, as defined by Dalton's Law. When people who live near sea level ascend to high altitude, the reduced inspired oxygen pressure decreases alveolar (P_AO_2) and arterial (P_aO_2) oxygen pressure, thus, oxygen saturation of hemoglobin (S_aO_2) and arterial oxygen content (C_aO_2) fall (2, 4). In response, cardiac output ($\dot{Q}$) during submaximal exercise increases at altitude as compared to sea level, maintaining oxygen delivery high enough to satisfy requirements of submaximal exercise. Maximal cardiac output ($\dot{Q}_{MAX}$), however, remains the same at high altitude as sea level, and is, therefore, achieved at lower exercise intensity and oxygen uptake level at altitude. Thus, as predicted by the Fick Equation, maximal oxygen uptake ($\dot{V}O_{2MAX}$) declines at high altitude proportionally to the reduction in C_aO_2 which, in turn, depends on the elevation ascended (4). On average, $\dot{V}O_{2MAX}$ falls 10% for every 1000 m ascended above 2000 m. This is the primary physiological mechanism for the degradation in aerobic power and endurance that unacclimatized lowlanders experience when they sojourn at high altitude.

Erythrocyte infusion ("blood doping") increases $\dot{V}O_{2MAX}$ at sea level (1, 7, 13-15). This effect is usually attributed to an increased C_aO_2 enabled by the greater hemoglobin concentration (13). Since the decrement in $\dot{V}O_{2MAX}$ at high altitude is proportional to the hypoxia-induced reduction in C_aO_2,

erythrocyte infusion could have ergogenic effects at high altitude equal or even greater than at sea level (10). Hypothetically, increasing the hemoglobin concentration before ascent to high altitude should enable C_aO_2 to be better maintained, despite the reduced S_aO_2, thus ameliorating the decrement in $\dot{V}O_2MAX$.

The physiological effects of erythrocyte infusion at high altitude have never been evaluated. Experiments studying erythrocyte infusion effects on maximal exercise responses during brief periods (i.e. < 60-min) of hypoxic gas breathing (8, 9), demonstrated a smaller decrement in $\dot{V}O_2MAX$ compared to placebo-infusion. Likewise, earlier experiments employing exposure to hypobaric hypoxia (6) noted lower heart rates during submaximal exercise in erythrocyte-infused subjects than in controls. These findings support the hypothesis that erythrocyte infusion might limit the decline in $\dot{V}O_2MAX$ with ascent to high altitude. However, brief periods of hypoxic exposure do not adequately simulate the ongoing physiological adjustments experience when lowlanders actually ascend to high altitude and remain.

Therefore, this study investigated whether infusing lowlanders with autologous erythrocytes before they ascended to high altitude attenuated the subsequent reduction in $\dot{V}O_2MAX$. Specifically, the hypothesis was that lowlanders infused with autologous erythrocytes before ascent would experience a smaller decline in their $\dot{V}O_2MAX$ at high altitude than subjects not infused with erythrocytes before ascent. A secondary goal was to deter-

mine if altitude acclimatization affected VO_{2MAX} of erythrocyte infused and non-infused lowlanders differently.

METHODS

Subjects and Experimental Design. Sixteen healthy men volunteered to participate as subjects after being informed of the requirements and risks associated with this research. The men were all soldiers assigned to the U.S. Army 10th Special Forces Group (Airborne), located at Fort Devens, MA. Table 1 depicts their physical characteristics.

TABLE 1 ABOUT HERE

Two units of blood were obtained from nine of these men by phlebotomy during the late winter and early spring months. One unit of blood was obtained on two occasions separated by five weeks. After each phlebotomy, the blood was separated into the erythrocyte and plasma components. The erythrocytes were then frozen with 40% (wt/vol) glycerol solution, and stored at -80°C. An eight week period separated the second phlebotomy and the beginning of the experimental phase of the study. Originally, eighteen subjects were phlebotomized, and the intent was to execute the study in a double-blind fashion. However, between the second phlebotomy and the beginning of experimental testing, nine men were reassigned to other duties and became unavailable to continue the study. Seven new subjects were recruited to participate, but the schedule allowed insufficient time for phlebotomy and recovery before the scheduled beginning of the experiments. Thus, these men were aware that they would not

receive erythrocytes during the study, while the original subjects were aware that eight out of nine of them would receive erythrocytes.

Each subject's height, weight, body density, maximal voluntary minute ventilation (MVV) and VO_2MAX were determined at sea level (SL: Natick, MA; 50 m). The subjects were then divided into two groups. The control (CON) group consisted of the seven non-phlebotomized subjects and one phlebotomized subject. The erythrocyte infused (ER) group consisted of the remaining phlebotomized subjects. As indicated in Table 1, the groups did not differ with respect to age, anthropomorphic measurements, or aerobic fitness as reflected by VO_2MAX. After completing sea-level testing, ER were infused with 700 ml of an autologous erythrocyte solution containing ~295 ml of erythrocytes, and CON were infused with 700 ml of a saline solution. Twenty-four hours later, the subjects traveled to high altitude (Pikes Peak, CO; 4300 m), arriving at about 2200 hours, eight hours after leaving sea level. The next day (HA1), VO_2MAX was measured (ten to fourteen hours after arrival at 4300 m). On HA2, MVV was measured. The subjects lived at high altitude for the next two weeks, completing additional testing and engaging in military mountaineering exercises. The VO_2MAX and MVV measurements were repeated again on the ninth (HA9) and tenth (HA10) day, respectively, of residence at 4300 m. After completing the altitude testing, the subjects returned to sea level, and VO_2MAX was measured within twenty-four hours after

descent.

Experimental Procedures. The MVV was measured according to standardized procedures (3). A computer controlled, dry-rolling seal spirometer system (Sensormedics 2450 Pulmonary Function Test System) was used to measure MVV at sea level and high altitude.

The VO_2MAX was determined using a progressive-intensity, continuous effort treadmill running protocol. Subjects first completed a 10-12 minute walk. During the first three minutes of the SL test, the walking speed and grade were adjusted to elicit 50-60% of the subject's age-predicted maximal heart rate. During tests on HA1 and HA9, the same speed and grade was used for the walk as in the SL trial. After a five minute rest, the subject then ran at 2.68 m/s continuously to exhaustion. The treadmill grade increased 2.5% every 100 seconds. The initial grade was 5% at SL, and 0% for the altitude tests. Heart rate and respiratory exchange parameters were measured every twenty seconds during both the walk and run. Heart rate was determined from the electrocardiogram recorded from three chest electrodes (CM 5 placement) and radio-telemetered to an oscilloscope-cardiotachometer (Hewlett-Packard). A Sensormedics 2900 Metabolic Measurement Cart measured VO_2, carbon dioxide output (VCO_2), and minute ventilation (VE). The VO_2MAX was determined by a plateau of VO_2, as defined by established criteria (5).

During the first SL test, and the HA1 and HA9 tests, arterial blood samples were obtained from a catheter placed in the radial artery before exercise. A slow drip infusion of

heparinized saline maintained catheter patency. A resting sample was drawn while the subject reclined quietly before each exercise test. A second sample (EX1) was drawn during the walk, after the subject had achieved a steady-state VO_2. The third (EX2) sample was drawn when the subject achieved about 80% VO_{2MAX} during the running portion of the test. This point was standardized between tests by drawing the blood sample at the same target heart rate during each test. That target heart rate was determined before the sea level test by taking 80% of the estimated heart rate reserve (age predicted maximal heart rate minus standing resting heart rate). The final arterial blood sample (MAX) was drawn from the subject coincident with exhaustion. This protocol allowed arterial blood to be sampled at two submaximal levels of exercise in addition to the resting and maximal exercise points. One submaximal level corresponded to the same absolute VO_2 during all three trials, while the other submaximal level corresponded to the same relative VO_2 (i.e. % altitude specific VO_{2MAX}) for all three trials. Arterial blood was collected in heparinized, gas impermeable syringes which were immediately capped and placed on ice for the brief period before it could be analyzed. Whole blood was analyzed in triplicate for microhematocrit (centrifugation), plasma protein (refractometry), lactate and glucose (YSI 2300 Analyzer) concentrations, and in duplicate for oxygen and carbon dioxide tensions (P_aO_2, P_aCO_2), pH, C_aO_2, $\%S_aO_2$, and hemoglobin concentration using the Radiometer ABL300 blood gas analyzer.

Data analyses. Student's t test for independent samples was used to evaluate the physical characteristics of the two groups of subjects (see Table 1) for significant differences. Multi-factor analysis of variance (ANOVA) was used to determine if the following factors had significant main or interactive effects: 1) group (2 levels); 2) trial (3 levels); or 3) exercise (3 or 4 levels). When the ANOVA indicated significant effects, Neuman-Keuls critical difference was used to compare means and locate significant differences between groups and among repeated measurements. A computerized statistical package (CSS:STAT-ISTICA, Statsoft Corp.) was used to analyze the data. Data are reported as means ± standard error. For all statistical procedures, significance was assumed when $P < 0.05$.

RESULTS

Cardiorespiratory Responses. Maximal voluntary ventilation did not differ between groups, either at SL or high altitude. MVV increased ($P < 0.01$) between SL (CON: 195±7; ER: 196±13 l/min, BTPS) to HA1 (CON: 234±10; ER: 245±12 l/min) with no further change on HA9 (CON: 246±9; ER: 252±12 l/min).

FIGURE 1 ABOUT HERE

Figure 1 depicts VO_2MAX at SL, before infusion, at high altitude, and twenty-four hours after descending to SL. Despite the tendency for a higher VO_2MAX in ER than CON on HA1, differences between groups were not significant either at sea level or high altitude. The decrement in VO_2MAX between SL and HA1 was not different for ER (25 ± 3%) and CON (28 ± 5%), and

acclimatization had no effect on the decrement. Upon descent, VO_{2MAX} returned to levels not different from those previously measured at SL.

FIGURE 2 ABOUT HERE

In Figure 2, VO_2, minute ventilation (V_E), and heart rate (HR) during submaximal and maximal exercise are expressed as a function of the relative exercise intensity (i.e., % of VO_{2MAX} at SL, HA1 and HA9). During submaximal exercise, VO_2 did not differ between ER and CON. The VO_2 during EX1 (walking) was unchanged from SL values during either HA1 or HA9 trials, and corresponded to 41% VO_{2MAX} at SL, compared ($P < 0.05$) to 56% VO_{2MAX} at both HA1 and HA9. The VO_2 during EX2 (submaximal running) was higher ($P < 0.01$) at SL than during either HA1 or HA9 trials (which did not differ), and corresponded to 84% VO_{2MAX} for all three trials.

There were no differences between ER and CON in V_E during exercise at SL, HA1 or HA9. For all three trials, V_E increased with exercise intensity. During submaximal (EX1, EX2) and maximal exercise, V_E and V_E/VO_2 (not shown) were both higher ($P < 0.01$) on HA1 than at SL, with an additional increase ($P < 0.05$) apparent on HA9 compared to HA1. At SL, V_E during maximal exercise corresponded to 88 ± 6 and 81 ± 3 %MVV for ER and CON ($P > 0.05$), respectively. During maximal exercise on HA1, V_E averaged 80 ± 4 and 82 ± 9 %MVV for ER and CON, respectively which was not different from SL values. During maximal exercise on HA9, V_E expressed as a fraction of MVV remained unchanged from SL values for both ER (79 ± 3 %MVV) and CON (84 ± 6 %MVV).

Despite a trend for lower HR in the ER at high altitude, HR did not differ between groups at SL, HA1 or HA9. During submaximal exercise on HA1, HR were higher ($P < 0.01$) than SL for a given absolute $\dot{V}O_2$, but unchanged when compared at the same relative intensity. On HA9, HR during submaximal exercise was reduced ($P < 0.01$) compared to HA1. On HA1, HR during maximal exercise averaged 8 b/min lower ($P < 0.01$) than at SL. On HA9, HR during maximal exercise was even lower ($P < 0.01$) than on HA1, averaging 27 b/min lower than SL.

TABLE 3 ABOUT HERE

Blood Oxygenation. Table 2 shows arterial blood gases and pH during rest and exercise at SL, HA1 and HA9. Arterial PO_2, PCO_2, and pH did not differ between groups during rest or exercise at sea level, HA1 or HA2. At HA1, P_aO_2 and P_aCO_2 during rest and each exercise intensity were lower ($P < 0.01$) than SL. Between HA1 and HA9, resting and exercise P_aO_2 levels increased ($P < 0.01$), whereas P_aCO_2 decreased ($P < 0.01$). Generally, exercise caused P_aO_2 and P_aCO_2 to decline ($P < 0.01$), although the pattern of response to increasing intensity differed slightly between SL, HA1 and HA9.

Arterial pH during rest and exercise were higher ($P < 0.01$) on HA1 and HA9 than at SL. At SL, pH fell ($P <0.01$) during submaximal exercise, and maximal exercise caused an additional fall ($P < 0.01$). On both HA1 and HA2, pH_a remained unchanged during submaximal exercise, but decreased ($P < 0.01$) with maximal exercise, however, the decrease in pH_a was less ($P < 0.05$)

pronounced on HA9 .

FIGURE 3 ABOUT HERE

Figure 3 depicts arterial hemoglobin, S_aO_2, and C_aO_2 during rest and exercise at SL, HA1 and HA9. At SL, none of these differed between CON and ER. On HA1, hemoglobin concentrations in ER had increased ($P < 0.01$) compared to SL and were higher ($P < 0.01$) than in CON. Hemoglobin concentrations in CON were not different from SL on HA1. Hemoglobin concentrations in ER remained unchanged on HA9 compared to HA1, whereas in CON, hemoglobin increased during this period, becoming different ($P < 0.06$) from SL on HA9. At HA1, S_aO_2 decreased ($P < 0.01$), compared to SL, with no differences between groups. Between HA1 and HA9, S_aO_2 increased ($P < 0.01$), however, it remained less ($P < 0.01$) than at SL, with no differences between groups. The C_aO_2 was lower ($P < 0.01$) at HA1 than at SL in both groups, but C_aO_2 remained higher ($P = 0.055$) in ER than CON. On HA9, C_aO_2 no longer differed between ER and CON, and had increased ($P < 0.01$) compared to HA1.

Exercise caused an increase ($P < 0.01$) in hemoglobin during all three trials. At SL, S_aO_2 remained unchanged during submaximal exercise, but slightly decreased ($P < 0.01$) with maximal exercise. At both HA1 and HA2, S_aO_2 decreased with submaximal exercise. At SL, C_aO_2 increased ($P < 0.01$) between rest and EX1, with no further change thereafter, whereas on HA1, C_aO_2 fell during exercise. By HA9, C_aO_2 did not fall during exercise.

FIGURE 4 ABOUT HERE

Figure 4 depicts arterial glucose (bottom row of panels) and lactate (top row of panels)concentrations during rest and exercise for each of the three trials. Glucose concentrations were higher ($P < 0.01$) in CON than ER during rest and exercise for all three trials. The difference, while statistically significant, was small, averaging only about 0.3 mmol/L, overall. Blood glucose concentrations were higher ($P < 0.01$) during rest and exercise on HA1 than either SL or HA9, when there were no differences. Glucose concentrations declined ($P = 0.056$) during all three exercise trials, but none of the paired comparisons between rest, EX1, EX2 or MAX achieved statistical significance. Lactate concentrations during rest and exercise did not differ between groups at SL, HA1 and HA9. Exercise increased arterial lactate concentrations over resting levels during all three trials. The increase in lactate over resting levels was significant by EX1 for HA1 but not until EX2 for SL or HA9. Lactate concentrations during EX2 and at MAX were similar for SL and HA1, but reduced on HA9.

DISCUSSION

This investigation studied the hypothesis that infusing autologous erythrocytes before ascent to high altitude would offset, to some degree, the usual decrement in VO_{2MAX} experienced by unacclimatized lowlanders rapidly deployed to high altitude. The experimental approach entailed infusing the autologous erythrocyte product of two units of blood or saline into low

altitude residents twenty-four hours before they ascended to altitude, and then comparing changes in maximal aerobic power on arrival and after nine days acclimatization. In earlier sea-level studies (12), this procedure induced about a 10% increase in hemoglobin concentration with a concomitant increase in VO_2MAX. Previous investigations attempting to evaluate erythrocyte infusion effects on responses to high altitude have studied exercise during brief periods in hypobaric chambers or while breathing hypoxic gas as opposed to actually ascending to high altitude and remaining. This study evaluated erythrocyte infusion effects under altitude conditions closely mimicking those in which this potential ergogenic procedure might really be employed.

The principal observations of the study do not support that hypothesis. The erythrocyte infusion procedure increased hemoglobin (~10%) as expected. However, the decrement in VO_2MAX after ascending from sea level to 4300 m altitude did not significantly differ between erythrocyte infused and saline infused subjects. The decrement in VO_2MAX for both groups combined, averaged about 26% compared to sea level, which is almost exactly what would be predicted from this laboratory's other studies of sea level residents sojourning at Pikes Peak (19). Thus, under the specific experimental conditions studied, autologous erythrocyte infusion did not ameliorate the decline in VO_2MAX at 4300 m altitude. However, it is probably inappropriate to conclude that erythrocyte infusion has no effect on VO_2MAX at

high altitude.

Despite the lack of statistical significance for the ANOVA's "group" factor, the data depicted in Figure 1 do suggest a trend for an erythrocyte infusion effect on the first day at altitude. The alternative statistical evaluations attempted (e.g. analysis of covariance) provided no further insight. Using the standard deviation of the VO_2MAX measurements, it can be calculated that twelve to twenty-one subjects would have been required in each group for a difference in VO_2MAX of the magnitude observed to have achieved statistical significance. Unfortunately, the sample size in this investigation was constrained by the maximum living capacity of the laboratory dormitory. With nine subjects per group, there is at least a 20% probability that the difference observed between groups was, in fact, real. Therefore, erythrocyte infusion effects on VO_2MAX which are too small to resolve by the methods employed cannot be ruled out, and rejection of the hypothesis may be unwarranted. However, notwithstanding statistical significance, effects this small probably have little practical significance.

The absence of an erythrocyte infusion effect on VO_2MAX in this study does not necessarily contradict studies suggesting an effect. Ergogenic effects of blood doping may diminish as altitude increases. Robertson et al. (8) reported that exposure to a simulated (hypoxic gas breathing) altitude of 2255 m, did not decrease VO_2MAX in subjects infused with 334 ml of autologous erythrocytes in contrast to the 10% reduction observed in the

same subjects during hypoxic exposure before infusion. In a separate study (9), exposure to a simulated altitude of 3566 m reduced VO_2MAX only 10% in subjects infused with 750 ml of autologous erythrocytes, compared to the 20% reduction observed before the infusion. Perhaps, erythrocyte infusion increases VO_2MAX at sea level, prevents hypoxic-related decrements in VO_2MAX at low (< 2500 m) altitudes (8), lessens but does not completely prevent declines in VO_2MAX at moderate (<3800 m) altitudes (9), and has negligible effects at higher altitudes (present study). Findings by others (16, 17) demonstrate that, as elevation increases, there is a progressive development of a pulmonary diffusion limitation during heavy exercise. A pulmonary diffusion limitation might preclude the benefit of an enhanced oxygen carrying capacity in the blood.

The ergogenic effects of increased erythrocyte volume on VO_2MAX are generally attributed to a facilitation of muscle oxygen delivery due to increased arterial oxygen content enabled by elevated hemoglobin concentration. That explanation may be overly simplistic since the improvement in VO_2MAX produced at sea level by erythrocyte infusion is not well correlated with corresponding increase in hemoglobin concentration (12). Further, that mechanism assumes that VO_2MAX is limited by systemic oxygen transport to muscle as determined by the cardiac output and arterial oxygen content. At high altitude, VO_2MAX may be limited by other factors. Despite enabling higher arterial oxygen content, erythrocyte infusion failed to alter the

decrement in VO_{2MAX} at 4300 m. Perhaps the extent of the effect on VO_{2MAX} produced by increased arterial oxygen content depends on the magnitude of the pressure gradient driving oxygen diffusion from the capillary into the tissue. Arterial oxygen pressure declines at altitude, and, in contrast to arterial oxygen content, arterial oxygen pressure was unaffected by erythrocyte infusion. This explanation is also consistent with the apparent graded decline in the infusion effect with increasing altitude.

Another possibility is that altitude acclimatization might negate erythrocyte infusion effects on VO_{2MAX}. Plasma volume normally declines markedly during altitude acclimatization, contributing to a fall in cardiac output (4). In Robertson et al.'s studies (8, 9) hypoxic exposure lasted under an hour, so acclimatization and the fall in plasma volume was not a factor. However, in the present study, the subjects had been at high altitude for ten to fourteen hours before VO_{2MAX} was measured. Plasma volume declined in both groups during this period, and plasma loss was more pronounced in erythrocyte infused compared to saline infused subjects (11). A decline in plasma (blood) volume might have limited maximal cardiac output, thereby offsetting effects of increased arterial oxygen content on VO_{2MAX}. Maximal cardiac output was not measured in this investigation, although there was a tendency (not significant) for maximal heart rates at altitude to be lower in the erythrocyte infused subjects.

Unacclimatized lowlanders accumulate more lactate during

exercise at a given absolute intensity at high altitude than at sea level, but when lactate accumulation is compared at similar relative exercise intensities (i.e. $\%VO_{2MAX}$), no altitude effect is apparent. This well known effect (18) of altitude exposure can be seen clearly in Figure 4, where lactate concentrations are higher on the first day at altitude compared to sea level during EX1 (same absolute VO_2), but no differences in lactate are seen comparing concentrations during EX2 or MAX. At sea level, lactate accumulation during exercise at a given VO_2 decreases following erythrocyte infusion (1). Therefore, it seemed reasonable to expect that erythrocyte infusion might ameliorate the increased lactate accumulation during exercise at altitude. That erythrocyte infusion did not alter lactate accumulation during exercise at altitude, further suggests that, oxygen delivery to active muscle tissue was not facilitated by the erythrocyte infusion despite the increased arterial oxygen content.

Pace et al. (6) demonstrated that heart rates during low intensity exercise at a simulated (hypobaric chamber) altitude of 4712 m were seven to fifteen b/min lower in subjects infused with 1000 ml of erythrocytes compared to control subjects. Heart rates of erythrocyte-infused subjects at this altitude were comparable to those of their control subjects exercising 1500 m lower. This observation gave rise to the concept that blood doping conferred an "altitude-lowering" effect. In the present investigation, heart rates during exercise at altitude tended to be lower in infused than control subjects, but the difference was

not significant. This may reflect higher exercise intensities used in this investigation than by Pace et al. (6), the greater volume of erythrocytes infused by those investigators (6), or acclimatization (i.e. plasma volume loss) effects in the present experiments.

In summary, this investigation examined the effects of autologous erythrocyte infusion on the decrement in VO_{2MAX} experienced by unacclimatized lowlanders rapidly transported to high altitude. Infusing erythrocytes on the day before ascent to altitude increased hemoglobin and hematocrit, and enabled arterial oxygen content to be maintained higher at 4300 m than in control subjects not receiving the extra erythrocytes. Despite the higher arterial oxygen content maintained during rest and exercise, the decrement in VO_{2MAX} was the same for infused and control subjects. In addition, the metabolic acidosis, respiratory compensation and blood glucose and lactate responses during submaximal and maximal exercise at high altitude were unaffected by erythrocyte infusion. The findings suggest that erythrocyte infusion effects on VO_{2MAX} are negligible or too small to detect at 4300 m, or that any such effects are offset by the on-going adjustments associated with altitude acclimatization.

Acknowledgments

The authors greatly appreciate the patience, effort and dedication of the soldiers of the US Army 10th Special Forces Group (Airborne) who volunteered to participate in this study. The assistance and cooperation of Commander and Staff of the 10th SFG were also instrumental in the execution of this project. The expert technical support provided by Beth Beidleman, Janet Laird, Michael Mackes, Linda Pivacek and Sinclair Smith is gratefully acknowledged.

The views, opinions, and/or findings reported in this manuscript are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation. Approved for public release; distribution is unlimited.

REFERENCES

1. Buick, F.J., N. Gledhill, A.B. Froese, L. Spriet, and E.C. Meyers. Effect of induced erythrocythemia on aerobic work capacity. *J. Appl. Physiol.* 48: 636-642, 1980.

2. Fulco, C.S., and A. Cymerman. Human performance and acute hypoxia. In: *Human Performance Physiology and Environmental Medicine at Terrestrial Extremes*, edited by K.B. Pandolf, M.N. Sawka, and R.R. Gonzalez. Indianapolis: Benchmark, 1988, p.467-495.

3. Gardner, R. M., J. L. Hankinson, J. L. Clausen, R. O. Crapo, R. L. J. Johnson, and G. R. Epler. Standardization of spirometry- 1987 update. *Am. Rev. Respir. Dis.* 136: 1285-1298, 1987.

4. Grover, R.F., J.V. Weil, and J.T. Reeves. Cardiovascular adaptation to exercise and high altitude. In: *Exer. Sport Sci. Rev.*, edited by K.B. Pandolf. New York: Macmillan, 1986, Vol.14, p.269-302.

5. Mitchell, J.H., B.J. Sproule, and C.B. Chapman. The physiological meaning of the maximal oxygen intake test. *J. Clin. Invest.* 37: 538-547, 1958.

6. Pace, N., E.L. Lozner, W.V. Consolazio, G.C. Pitts, and L.J. Pecora. The increase in hypoxia tolerance of normal men accompanying the polycythemia induced by transfusion of

erythrocytes. *Am. J. Physiol.* 148: 152-163, 1947.

7. Robertson, R. J., R. Gilcher, K.F. Metz, C.J. Caspersen, T.G. Allison, R.A. Abbott, G.S. Skrinar, J.R. Krause, and P.A. Nixon. Hemoglobin concentration and aerobic work capacity in women following induced erythrocythemia. *J. Appl. Physiol.* 57: 568-575, 1984.

8. Robertson, R.J., R. Gilcher, K.F. Metz, C.J. Caspersen, T.G. Allison, R.A. Abbott, G.S. Skrinar, J.R. Krause, and P.A. Nixon. Effect of simulated altitude erythrocythemia in women on hemoglobin flow rate during exercise. *J. Appl. Physiol.* 64: 1644-1649, 1988.

9. Robertson, R.J., R. Gilcher, K.F. Metz, G.S. Skrinar, T.G. Allison, H.T. Bahnson, R.A. Abbott, R. Becker, and J.E. Falkel. Effect of induced erythrocythemia on hypoxia tolerance during physical exercise. *J. Appl. Physiol.* 53: 490-495, 1982.

10. Sawka, M.N., and A.J. Young. Acute polycythemia and human performance during exercise and exposure to extreme environments. In: *Ex. Sports Sci. Rev.*, edited by K. B. Pandolf. Baltimore: Williams and Wilkens, 1989, p. 265-293.

11. Sawka, M.N., A.J. Young, R. Boushel, T. Lyons, P.B. Rock, B.J. Freund, S.R. Muza, C. Fulco, A. Cymerman, K.B. Pandolf, L.E. Pivacek, and C.R. Valeri. Erythrocyte reinfusion effects on

vascular volume & erythropoietin at high altitude. *Med. Sci. Sports. Exer.* 27: S109, 1995 (abstract).

12. Sawka, M.N., A.J. Young, S.R. Muza, R.R. Gonzalez, and K.B. Pandolf. Erythrocyte reinfusion and maximal aerobic power: examination of modifying factors. *JAMA* 257: 1496-1499, 1987.

13. Spriet, L.L. Blood doping and oxygen transport. In: *Perspectives in Exercise Science & Sports Medicine, Vol 4, Ergogenics-Enhancement of Performance*, edited by D.R. Lamb, and M.H. Williams. Indianapolis: Brown & Benchmark, 1991, p. 213-248.

14. Spriet, L.L., N. Gledhill, A.B. Froese, and D.L. Wilkes. Effect of graded erythrocythemia on cardiovascular and metabolic responses to exercise. *J. Appl. Physiol.* 61: 1942-1948, 1986.

15. Thomson, J.M., J.A. Stone, A.D. Ginsburg, and P. Hamilton. Oxygen transport during exercise following blood reinfusion. *J. Appl. Physiol.* 53: 1213-1219, 1982.

16. Wagner, P. D., J. R. Sutton, J. T. Reeves, A. Cymerman, B. M. Groves, and M. K. Malconian. Operation Everest II: pulmonary gas exchange during a simulated ascent of Mt. Everest. *J. Appl. Physiol.* 63: 2348-2359, 1987.

17. West, J.R., S. Lahiri, M.B. Gill, J.S. Milledge, L.G.C.E. Pugh,

and M.P. Ward. Arterial oxygen saturation during exercise at high altitude. *J. Appl. Physiol.* 17: 617-621, 1962.

18. Young, A.J. Energy substrate utilization during exercise in extreme environments. In: *Exerc. Sport Sci. Rev.*, edited by K. B. Pandolf, and J. O. Holloszy. Baltimore, MD: Williams and Wilkens, 1990, p. 65-117.

19. Young, A.J., A. Cymerman, and R.L. Burse. The influence of cardiorespiratory fitness on the decrement in maximal aerobic power at high altitude. *Eur. J. Appl. Physiol.* 54: 12-15, 1985.

FIGURE LEGENDS

Figure 1. Effect of high altitude (4300 m) on the maximal oxygen uptake (mean ± SE) of sea-level residents infused with autologous erythrocytes (ER) or saline (CON) the day before they ascended.

Figure 2. Effect of high altitude (4300 m) on heart rate, minute ventilation and oxygen uptake (means ± SE) during submaximal and maximal exercise in sea-level residents infused on the day before they ascended with autologous erythrocytes (ER) or saline (CON).

Figure 3. Effect of high altitude (4300 m) on arterial hemoglobin concentration ($[Hb_a]$), oxygen saturation of hemoglobin (S_aO_2) and oxygen content (C_aO_2) during submaximal and maximal exercise (means ± SE) in sea-level residents infused with autologous erythrocytes (ER) or saline (CON) on the day before they ascended.

Figure 4. Effect of high altitude (4300 m) on arterial lactate and glucose concentration (means ± SE) during submaximal and maximal exercise in sea-level residents infused with autologous erythrocytes (ER) or saline (CON) on the day before they ascended.

Table 1. Physical characteristics of subjects.

GROUP	AGE (yrs)	HT (cm)	WT (kg)	A_D (m^2)	BF (%)	VO_2MAX ($l \bullet min^{-1}$)	VO_2MAX ($ml \bullet kg^{-1} \bullet min^{-1}$)
CON (n = 8)	31 ±1	177 ±2	83.2 ±2.5	2.0 ±0.1	20.1 ±1.7	4.33 ±0.14	52.2 ±1.6
ER (n = 8)	30 ±1	180 ±3	82.1 ±3.2	2.0 ±0.1	17.0 ±1.1	4.44 ±0.12	54.3 ±1.1

Means (±) SE of age, height (HT), weight (WT), body surface area (A_D), percent body fat (BF) and maximal oxygen uptake (VO_2MAX) of control (CON, saline infused) and experimental (ER, erythrocyte infused) subjects did not differ significantly (t test, $P > 0.05$).

TABLE 2. Arterial blood gases and pH.

		P_aO_2, torr		P_aCO_2, torr		pH_a	
		CON	ER	CON	ER	CON	ER
SL	REST	103 ± 2	106 ± 3	36 ± 2	32 ± 1	7.42 ± 0.01	7.43 ± 0.01
	EX1	97 ± 2	98 ± 2	39 ± 1	36 ± 1	7.40 ± 0.01	7.41 ± 0.01
	EX2	92 ± 3	90 ± 4	34 ± 1	34 ± 1	7.41 ± 0.01	7.37 ± 0.02
	MAX	93 ± 3	94 ± 3	32 ± 1	29 ± 2	7.30 ± 0.02	7.25 ± 0.02
HA1	REST	47 ± 2	48 ± 2	26 ± 1	25 ± 1	7.49 ± 0.01	7.49 ± 0.01
	EX1	37 ± 1	37 ± 1	25 ± 1	26 ± 1	7.47 ± 0.01	7.46 ± 0.01
	EX2	37 ± 1	37 ± 1	22 ± 1	21 ± 1	7.49 ± 0.01	7.47 ± 0.01
	MAX	39 ± 2	39 ± 2	20 ± 1	19 ± 1	7.34 ± 0.02	7.30 ± 0.02
HA9	REST	53 ± 2	52 ± 1	21 ± 1	21 ± 1	7.49 ± 0.01	7.48 ± 0.01
	EX1	45 ± 1	44 ± 1	22 ± 1	22 ± 1	7.48 ± 0.01	7.46 ± 0.02
	EX2	45 ± 1	45 ± 1	19 ± 1	19 ± 1	7.52 ± 0.01	7.48 ± 0.02
	MAX	47 ± 2	44 ± 1	17 ± 1	18 ± 1	7.35 ± 0.03	7.34 ± 0.02

Values are means (± SE) of arterial oxygen (P_aO_2) and carbon dioxide pressures (P_aCO_2), and pH for control (CON) and experimental (ER) subjects at sea level (SL) and high altitude (4300 m) on the first (HA1) and ninth (HA9) day during rest, two intensities of submaximal exercise (EX1, EX2) and maximal exercise (MAX).

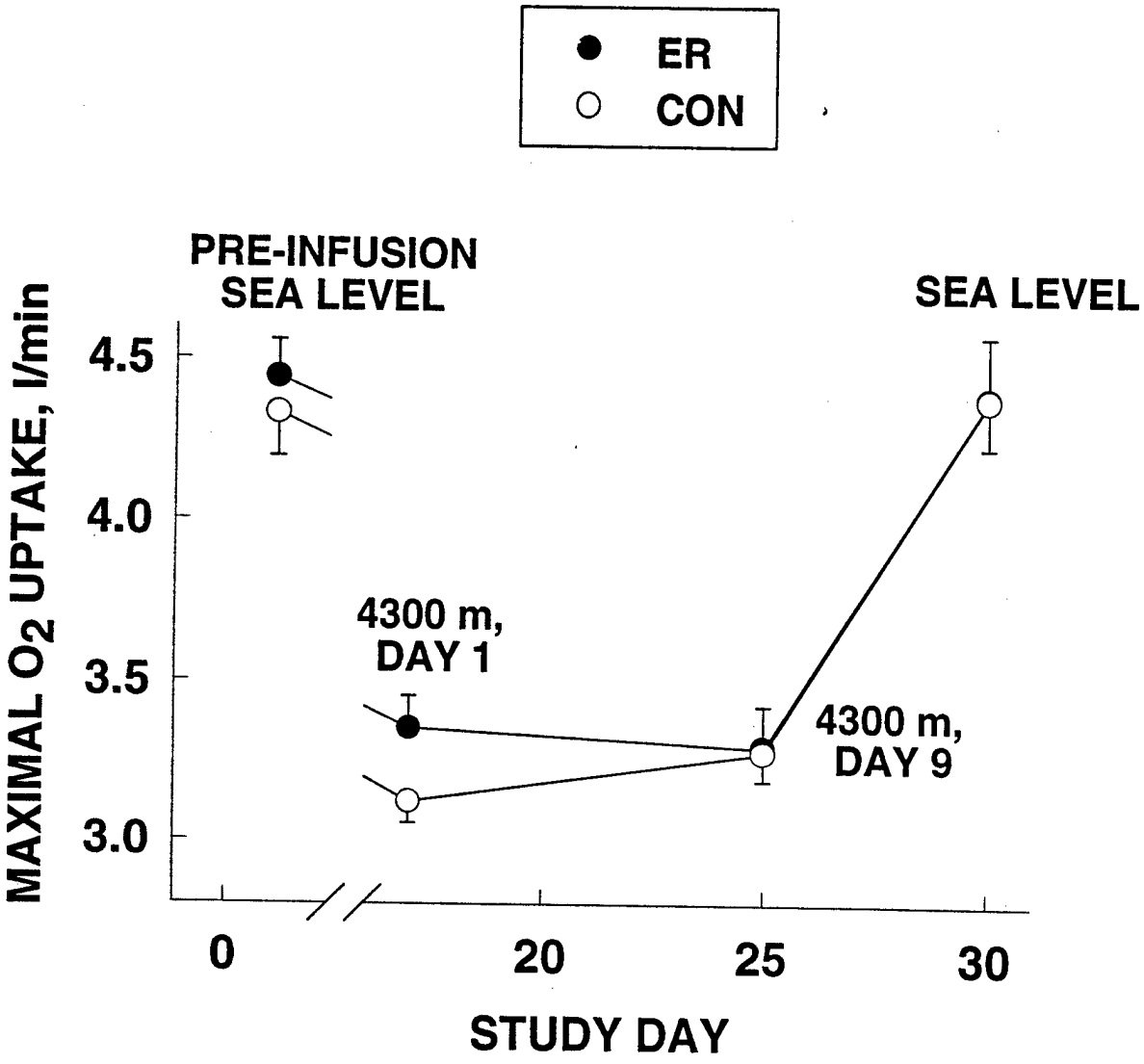

ER
CON
PRE-INFUSION
SEA LEVEL
SEA LEVEL
4.5
4.0
3.5
3.0
MAXIMAL O_2 UPTAKE, l/min
4300 m,
DAY 1
4300 m,
DAY 9
0
20
25
30
STUDY DAY

Figure 2.

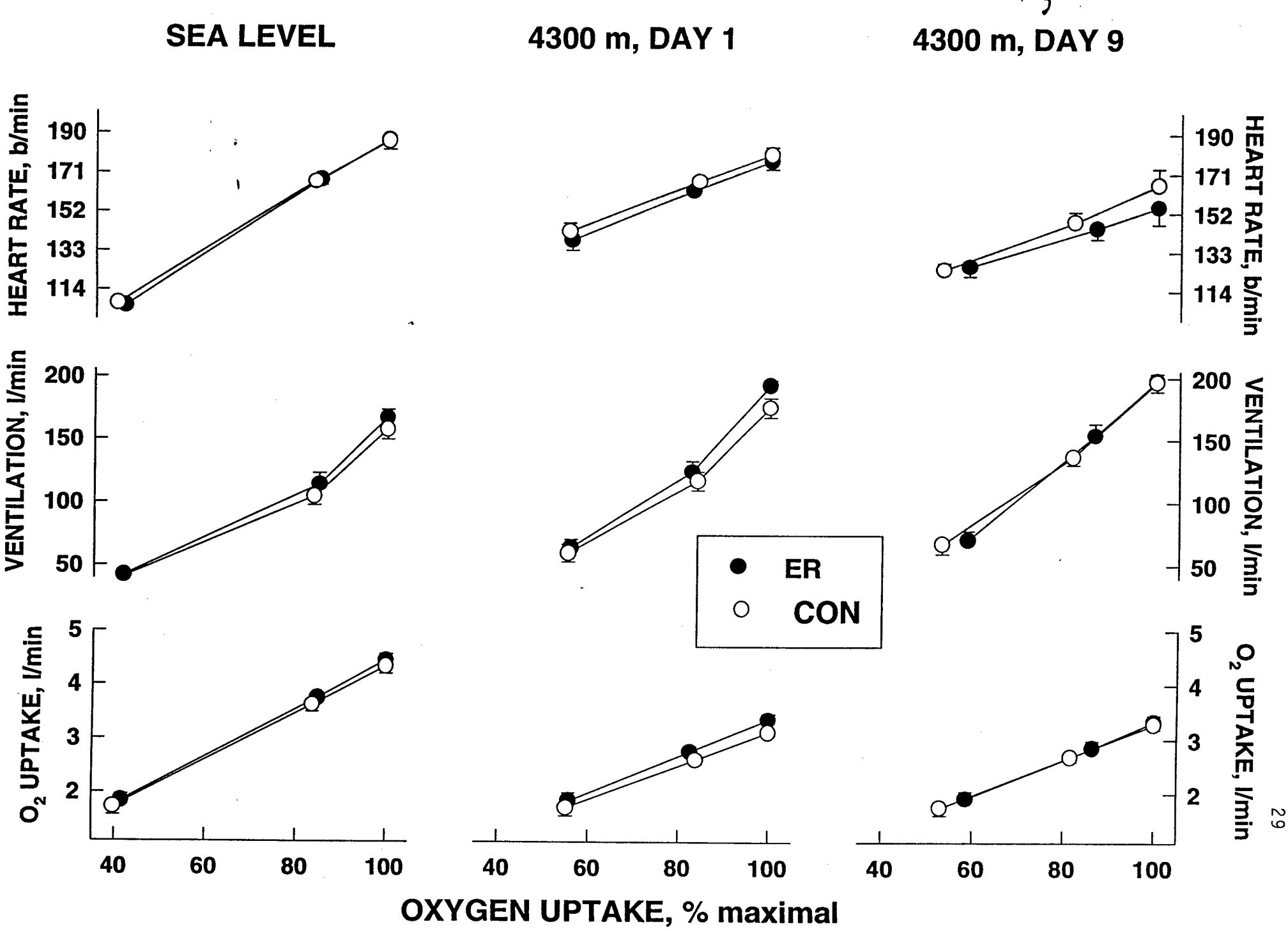

SEA LEVEL
4300 m, DAY 1
4300 m, DAY 9
HEART RATE, b/min
190
171
152
133
114
VENTILATION, l/min
200
150
100
50
O2 UPTAKE, l/min
5
4
3
2
ER
CON
40
60
80
100
OXYGEN UPTAKE, % maximal

Figure 3.

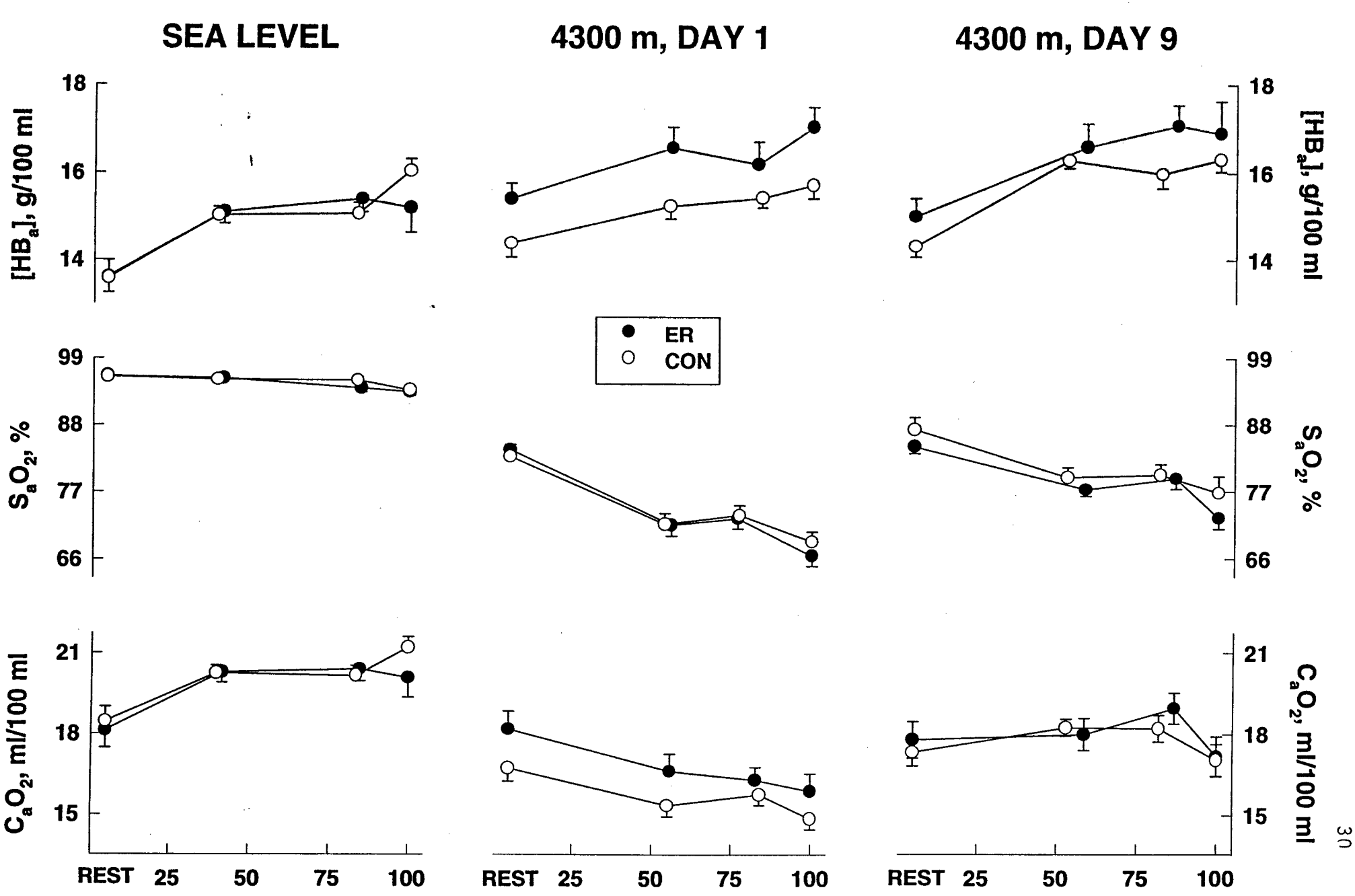
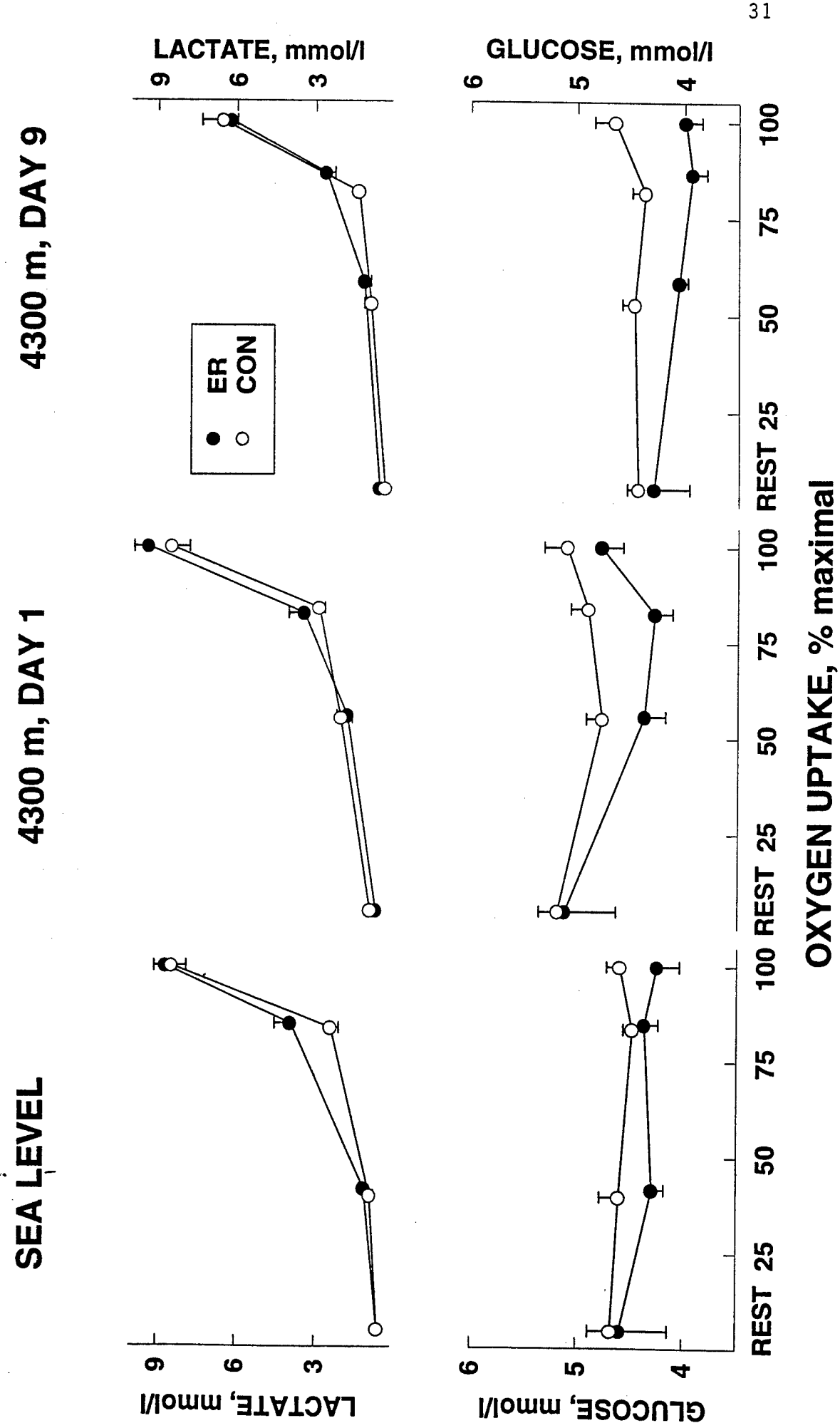

SEA LEVEL
4300 m, DAY 1
4300 m, DAY 9
[HBa], g/100 ml
SaO2, %
CaO2, ml/100 ml
ER
CON
18
16
14
99
88
77
66
21
18
15
REST
25
50
75
100
OXYGEN UPTAKE, % maximal

Figure 4.


SEA LEVEL
4300 m, DAY 1
4300 m, DAY 9
LACTATE, mmol/l
GLUCOSE, mmol/l
ER
CON
REST 25 50 75 100
OXYGEN UPTAKE, % maximal